P ENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 04 October 2000 (04.10.00)	
International application No. PCT/HU00/00009	**Applicant's or agent's file reference** 91042-10864
International filing date (day/month/year) 28 January 2000 (28.01.00)	**Priority date** (day/month/year) 01 February 1999 (01.02.99)
Applicant BOGYE, Gábor	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

29 August 2000 (29.08.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Henrik Nyberg
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

14

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
91042-10864		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/HU00/00009	28/01/2000	01/02/1999
International Patent Classification (IPC) or national classification and IPC A61K31/505		
Applicant BOGYE, Gábor		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29/08/2000	10.05.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Blott, C Telephone No. +49 89 2399 7538

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/HU00/00009

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-10 as originally filed

Claims, No.:

1-8 with telefax of 06/03/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-8.

because:

   ☒ the said international application, or the said claims Nos. 1-8 (with regard to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 6-8 are so unclear that no meaningful opinion could be formed (*specify*):
   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-5
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-5
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	see separate sheet

No: Claims

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

SECTION III

1. Claims 1-8 relate to a subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT).

2. The subject-matter of claim 7 lacks clarity since it refers to "...a composition as claimed in claim 1...", although claim 1 is not directed to a composition (Art. 6 PCT). Furthermore, claim 7 refers to a method of treatment but does not specify the disease which has to be treated (Art. 6 PCT). The latter also applies to claim 8.

3. Claim 6 does not contain all the features of claim 1 and is therefore not dependent on claim 1 (Art. 6 PCT).

SECTION V

4. a) The following documents, which were cited in the International Search Report, are referred to in this report; the numbering will be adhered to in the rest of the procedure:

   D1: JOURNAL OF WOMEN'S HEALTH AND GENDER-BASED MEDICINE, 1999, 8/9, pages 1167-1172

   D2: GB 2 131 292

   D3: JOURNAL OF THE AMERICAN COLLEGE OF NUTRITION, vol. 2, no. 3, 1983, pages 221-230, ISSN: 0731-5724

   D4: AMERICAN JOURNAL OF CLINICAL NUTRITION, vol. 35, no. 1, January 1982, pages 73-82

   D5: THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, vol. 226, no. 12, 17 December 1973, pages 1421-1424, ISSN: 0098-7484

   The following documents have been cited by the applicant in the description; the numbering will be adhered to in the rest of the procedure:

   D6: JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, vol. 277, No. 22, June 1997, pages 1775-1781

   D7: New England Journal of Medicine, vol. 334, March 1996, No. 12, pages 759-762

   D8: AMERICAN JOURNAL OF CLINICAL NUTRITION, vol. 65, No. 2, February

1997, pages 572-573

b) Contrary to what was stated in the International Search Report, D1 was published between the priority date and the filing date of the present application. The priority document was not available when this report was issued. It is assumed that the priority right is valid for all the parts of the present application. The IPEA reserves the right to modify this opinion when the priority document will be available.
In the following procedure, it will be assumed, that D1 is not a document of the prior art (Rule 33.1 PCT).

c) D2 refers to pharmaceutical formulations comprising a progestationally agent, such as progesterone, and folic acid (cf. claim 1 and page 2, line 31). The formulations may further comprise e.g. vitamin B_6 or B_{12} (cf. page 2, lines 52-65). The combinations are used in the treatment of men to reduce hair loss (cf. page 1, lines 5-6). D2 does not refer to the reduction of homocysteine plasma levels nor the risk of thromboembolic side effects induced by the hormone.

d) D3 refers to a study wherein both folate from orange juice and synthetic folic acid increased serum folate concentration in women ingesting a folate restricted diet. Women using combination type oral contraceptives (OCA) had lower folate serum than non-users at the inception of the study. D3 does not refer to the reduction of homocysteine plasma levels nor the risk of thromboembolic side effects induced by gestagen hormones.

e) D4 refers a clinical trial wherein the manifestation of dysplasia and megaloblastis in uterine cervix improved after folic acid supplementation in women using combination type OCAs (cf. abstract and page 79, left column, lines 15-20 from the bottom). OCA users had lower red cell folate values and plasma B_{12} levels than non-users (cf. abstract and page 78, right column, lines 14-18). D4 does not refer to the reduction of homocysteine plasma levels nor the risk of thromboembolic side effects induced by gestagen hormones.

f) D5 refers to a study wherein the treatment with folic acid reverted to normal or improved megaloblastic abnormalities of cervicovaginal cells similar to those seen in severe folate and vitamin B_{12} deficiency, in women taking OCAs (combination type

or progestogens only) (cf. abstract). In this study, 17-21% of the women had decreased serum folate concentration. D5 does not refer to the reduction of homocysteine plasma levels nor the risk of thromboembolic side effects induced by gestagen hormones.

g) D6 refers to a study wherein elevated plasma homocysteine level was shown to be a risk factor for artherosclerotic vascular diseases (cf. abstract). It also increases the risk associated with smoking and hypertension (cf. abstract). Plasma homocysteine concentrations relates inversely to blood levels of folate, cobalamin and pyridoxine and to intakes of these vitamins (cf. page 1780, left column, lines 5-14). D6 does not refer to the risk of thromboembolic side effects induced by gestagen hormones.

h) D7 refers to a study wherein it was shown that high plasma homocysteine levels are a risk factor for deep-vein thrombosis (cf. abstract). Elevated plasma homocysteine levels may result from low levels of folic acid, vitamin B_6 or B_{12}. According to the authors of D7, it remains to be tested wether homocysteine-lowering therapy with vitamins can prevent recurrent venous thrombosis (cf. page 762, left column, line 13 from the bottom, to end of document).

i) According to D8, supplements comprising folate associated with vitamin B_{12} may be used for the prevention of vasculotoxic hyperhomocysteinemia and thereby the prevention of thrombotic strokes and peripheral venous thromboses (cf. page 572, right column, lines 22-29).

5. Novelty

a) None of the above-mentioned documents discloses nor anticipates the use of a plasma homocysteine content reducing agent in compositions comprising a gestogen type hormone, for the reduction of thromboembolic side effect risk induced by the hormone. The subject-matter of claim 1 consequently is new over the prior art (Art. 33(2) PCT).

b) Item 5.a) also applies to dependent claims 2-5.

c) Claim 6: cf. section III 3.

The use of a plasma homocysteine reducing agent simultaneously, previously or subsequently with a gestogen type hormone for the reduction of thromboembolic side effect risk induced by the hormone is neither disclosed nor anticipated by D1-8.

6. Inventive step

a) Document D5, which is considered to represent the most relevant state of the art, refers, as already mentioned under section V 4.f), to a study wherein the treatment with folic acid reverted to normal or improved megaloblastic abnormalities of cervicovaginal cells similar to those seen in severe folate and vitamin B_{12} deficiency, in 115 healthy women taking OCAs (combination type or progestogens only). In this study, 17-21% of the women had decreased serum folate concentration.

The problem to be solved by the present invention can be regarded as the reduction of thromboembolic side effects induced by gestogen hormones.

The solution of said problem according to the present application is the use of a plasma homocysteine content reducing agent in compositions comprising the gestogen type hormone.

It is already known from D7 that low levels of folic acid, vitamin B_6 or B_{12} induce elevated plasma homocysteine levels, which are a risk factor for thromboses. According to the authors of D7, homocysteine-lowering therapy with vitamins may prevent recurrent venous thrombosis.

In the study of D5, only 17-21% of the women taking OCAs (combination type or progestogens only) had decreased serum folate concentration. It is therefore not possible, on the basis of D5 in combination with D7, to conclude that gestogen type hormone systematically lead to subnormal levels of folic acid and consequently to elevated plasma homocysteine levels, which are responsible for an increased risk for thromboses. Furthermore, the applicant confirmed with telefax of 06/03/01, that most patients did not have decreased serum folate concentrations or that there was no relationship between the elevated plasma homocysteine levels and the serum folate concentrations in the examples of the present application.

It is therefore not derivable from D5, alone or in combination with any of the other cited documents, that gestogen type hormones increase plasma homocysteine levels and, as a consequence, the thromboembolic side effect risk.

The use of a plasma homocysteine reducing agent such as folic acid, vitamin B_6 or B_{12} in compositions comprising a gestogen type hormone for the reduction of thromboembolic side effect risk induced by the hormone is consequently not evident to the skilled man.

Thus, the subject-matter of claims 1-5 involves an inventive step (Art. 33(3) PCT).

7. Industrial applicability

For the assessment of present claims 1-8 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

SECTION VIII

8. The description is not in line with the amended claims filed with telefax of 06.03.2001 (Art. 6 PCT).

9. The format of claim 1 is not clear (method of treatment, subsequent therapeutic application...) (Art. 6 PCT).

Claims

1. Use of a plasma homocysteine content reducing agent in compositions comprising a gestogen type hormone for the reduction of thromboembolic side effect risk induced by the hormone.

2. Use as claimed in claim 1, comprising using as plasma homocysteine content reducing agent an efficient amount of folic acid, vitamin B_6, vitamin B_{12}, betaine, choline, acetyl cysteine, metabolic precursors, analogues and/or derivatives thereof.

3. Use as claimed in claim 1, comprising using as plasma homocysteine content reducing agent an efficient amount of folic acid.

4. Use as claimed in claim 1, comprising using as plasma homocysteine content reducing agent an efficient amount of vitamin B_6.

5. Use as claimed in claim 1, comprising as gestogen type hormone an efficient amount of progesterone type hormone(s), metabolic precursor(s), analogue(s) and/or derivative(s) thereof.

6. Use as claimed in claim 1, comprising using the plasma homocysteine content reducing agent simultaneously, previously or subsequently with gestogen type hormone.

7. Method of treatment of patients taking gestogen type hormone compositons, which comprises administration of an effective dosage of a composition as claimed in claim 1.

8. Method of treatment of patients taking gestogen type hormone compositons, which comprises administration of an effective amount of plasma homocysteine content reducing agents, selected from folic acid, vitamin B_6, vitamin B_{12}, betaine, choline, acetyl cysteine, metabolic precursors, analogues and/or derivatives thereof.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
91042-10864		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/HU 00/00009	28/01/2000	01/02/1999
Applicant		
BOGYE, Gábor		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   PHARMACEUTICAL COMBINATION OF PROGESTERONE AND FOLIC ACID

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

Claims:

1. Pharmaceutical composition based on gestogen type hormone, comprising next to the hormone component component(s) reducing the plasma homocysteine content increased upon taking hormone.
2. Pharmaceutical composition as claimed in claim 1, comprising an efficient amount of plasma homocysteine content reducing agent selected from folic acid, vitamin B_6, vitamin B_{12}, betaine, choline, acetyl cysteine and metabolic precursors, analogues and/or derivatives thereof.
3. Pharmaceutical composition as claimed in claim 1, comprising as plasma homocysteine content reducing agent an efficient amount of folic acid.
4. Pharmaceutical composition as claimed in claim 1, comprising as plasma homocysteine content reducing agent an efficient amount of vitamin B_6.
5. Pharmaceutical composition as claimed in claim 1, comprising an efficient amount of hormone selected from progesterone type hormone(s), metabolic precursor(s), analogue(s) and/or derivative(s) thereof.
6. Use of plasma homocysteine content reducing agents selected from folic acid, vitamin B_6, vitamin B_{12}, betaine, choline, acetyl cysteine and metabolic precursors, analogues and/or derivatives thereof for the preparation of pharmaceutical composition containing gestogen type hormone(s) reducing the plasma homocysteine level.
7. Use of folic acid for the preparation of pharmaceutical composition containing gestogen type hormone(s) reducing the plasma homocysteine level.
8. Use of vitamin B_6 for the preparation of pharmaceutical composition containing gestogen type hormone(s) reducing the plasma homocysteine level.

9. Process for reducing the plasma homocysteine level, which comprises administering a pharmaceutical composition containing gestogen type hormone simultaneously or previosuly or subsequently with an effiecient amount of plasma homocysteine content reducing agent, selected from folic acid, vitamin B_6, vitamin B_{12}, betaine, choline, acetyl cysteine and metabolic precursors, analogues and/or derivatives thereof.

10. Process for reducing the plasma homocysteine level, which comprises administering a pharmaceutical composition containing gestogen type hormone simultaneously or previosuly or subsequently with an effiecient amount of folic acid.

11. Process for reducing the plasma homocysteine level, which comprises administering a pharmaceutical composition containing gestogen type hormone simultaneously or previosuly or subsequently with an effiecient amount of vitamin B_6.

12. Use of plasma homocysteine content reducing agents, selected from folic acid, vitamin B_6, vitamin B_{12}, betaine, choline, acetyl cysteine and metabolic precursors, analogues and/or derivatives thereof for reducing the plasma homocysteine content.

13. Use of folic acid for reducing the plasma homocysteine content increased by gestogen hormones.

14. Use of vitamin B_6 for reducing the plasma homocysteine content increased by gestogen hormones.

15. Method of treatment of patients taking gestogen type hormone compositons, which comprises administration of an effective dosage of a composition as claimed in claim 1.

16. Method of treatment of patients taking gestogen type hormone compositons, which comprises administration of an effective amount of plasma homocysteine content reducing agents, selected from folic acid, vitamin B_6, vitamin B_{12}, betaine, choline, acetyl cysteine and metabolic precursors, analogues and/or derivatives thereof.

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International Bureau

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(74) Agent: DANUBIA PATENT AND TRADEMARK ATTORNEYS; Bajcsy–zsilinszky út 16, H–1051 Budapest (HU).

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Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PHARMACEUTICAL COMBINATION OF PROGESTERONE AND FOLIC ACID

(57) Abstract

The present invention relates to pharmaceutical composition(s) comprising gestogen type steroid hormone(s) and compound(s) lowering in human plasma the level of homocysteine, capable of lowering the risk of thromboembolic side effects of gestogen type compositions. The plasma homocysteine content reducing agents may be selected from folic acid, vitamin B_6, vitamin B_{12}, betaine, choline, acetyl cysteine and metabolic precursors, analogues and/or derivatives thereof. The invention is also directed to the use of said plasma reducing agents.

FOR THE PURPOSES OF INFORMATION ONLY

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PHARMACEUTICAL COMBINATION OF PROGESTERONE AND FOLIC ACID

The present invention relates to pharmaceutical composition(s) comprising gestogen type steroid hormone(s) and compound(s) lowering in human plasma the level of homocysteine, capable of lowering the risk of thromboembolic side effects of gestogen type compositions.

It has been known that the most important side effect of the use of some compositions containing steroid hormones, such as gestogen, is the increased occurrence of thromboembolic diseases. These side effects may occur upon the administration of any pharmaceutical composition comprising gestogen type hormone and they are often lethal.

This problem has been solved so far by two methods:

a) Patients, in case of which the probability of the occurrence of thromboembolic side effects is rather high (adipose, smokers, patients of the age above 35, patients whose anamnesis already showed thromboembolic disease), were excluded from this hormone therapy.
b) On the basis of the positive correlation of the occurrence of the thromboembolic complications and the dose of the used hormone by decreasing the hormone content of the pharmaceutical compositions the occurrence of the thromboembolic complications could be reduced.

These known methods show numerous disadvantages:
The patients excluded from the hormone therapy on the basis of the absolute and relative contraindications, could not obtain an otherwise necessary treatment.

By reducing the hormone content of the given pharmaceutical composition, not only the occurrence of the side effects is reduced, but the extent and safety of the effect to be achieved, too.

A further disadvantage of this latter known method is that although the risk of the occurrence of the side effects is reduced, the potentially lethal side effects cannot be entirely eliminated.

There is a continuous need for such novel compositions, the use of which results in a lower risk of thromboembolic diseases than with the known compositions, while maintaining the original activity of the hormone(s).

On the basis of recent research it has become known, that the increase of the homocysteine content in the human plasma is an independent risk factor of arterial and venal thrombosis and embolism. We refer to the latest studies summarising this problem: *(Welch GN, Loscalzo J. Homocysteine and atherothrombosis. N Engl J Med 1998, 338:1042-50.; den Heijer M, Kostor T, Blom HJ, et al. Hyperhomocysteinemia as a risk factor for deep-vein thrombosis. N Engl J Med 1996, 334:759-62.; Graham IM, Daly IE, Refsum H, et al. Plasma homocysteine as a risk factor for vascular disease. JAMA 1997, 277:1775-81.).*

In EP 0347864 A2 (Strydom, Andries Johannes Cornelus: Anti-atherogenic agents) the authors disclose that atherosclerosis can be reduced by using some pharmaceutical compositions reducing the homocysteine content of the plasma and/or arterial wall.

As opposed to the contents of said patent specification, we have recognised that the increased homocysteine content of the plasma itself induces susceptibility to thromboembolism before leading to atherosclerosis. Therefore the aim of our invention was not only to

prevent or reduce atherosclerosis by reducing the homocysteine content in the plasma, but to achieve the prevention of thromboembolism occurring independently of atherosclerosis.

Some compounds (folic acid, vitamin B_6, vitamin B_{12}, betaine, choline, acetyl cysteine) reduce the homocysteine content of the plasma in case of certain types of hyperhomocysteinaemia (not all types). (Welch GN, Loscalzo J. Homocysteine and atherothrombosis. N Engl J Med 1998, 338:1042-50.; Refsum H, Ueland PM. Clinical significance of pharmacological modulation of homocysteine metabolism. TiPS 1990, 11:411-6.)

In case of some of these vitamins B (folic acid, vitamins B_6 and B_{12}), it can be considered as proven that they reduce the occurrence of thromboembolic complications not induced by medicines.

(Graham IM, Daly IE, Refsum H, et al. Plasma homocysteine as a risk factor for vascular disease. JAMA 1997, 277:1775-81.; Herbert V, Bigaouette J. Call for endorsement of a petition to the Food and Drug Administration to always add vitamin B12 to any folate fortification or supplement. Am J Clin Nutr 1997, 65:572-3.).

In case of steroid hormones containing ostrogen, it has been already suggested that these hormones tend to make susceptible to thromboembolism through the increase of the homocysteine content of the plasma, but this hypothesis could not be proved by tests carried out so far. (*Brattstrom L, Israelsson B, Olsson A, Andersson A,. Hultberg B. Plasma homocysteine in women on oral oestrogen-containing contraceptives and in men with oestrogen-treated prostatic carcinoma. Scand J Clin Invest 1992, 52:283-7.).*

We have now surprisingly found that the occurrence of thromboembolic diseases which can be correlated with the administration of pharmaceutical compositions containing gestogen type steroid hormone, is greatly due to the plasma homocysteine level increasing activity of the gestogen hormones. We have further recognised that this increase of the plasma homocysteine level

caused by gestogen hormones can efficiently be reduced or prevented by known homocysteine level reducing agents, e.g. folic acid, vitamin B_6, vitamin B_{12}, betaine, choline, acetyl cysteine and metabolic precursors, analogues and/or derivatives thereof.

According to the invention there is provided a solution to the above-mentioned aim, we can reduce the increased homocysteine level or prevent the increase thereof induced by certain gestogen type hormones independently from atherosclerosis. This decrease or prevention can be achieved by such homocysteine level reducing agents, which have not been used for this purpose so far.

The present invention provides pharmaceutical composition(s), which reduce(s) the risk of the thromboembolic side effects of gestogen hormone containing medicines.

The pharmaceutical composition(s) according to the invention comprise an efficient amount of gestogen type steroid hormone(s), metabolic precursor(s), analogue(s) and /or derivative(s) thereof, and an efficient amount of plasma homocysteine level reducing compound(s) e.g. folic acid, vitamin B_6, vitamin B_{12}, betaine, choline, acetyl cysteine and metabolic precursors, analogues and/or derivatives thereof.

It is a favourable feature of the pharmaceutical compositions according to the invention that the hormone component(s) thereof is (are) suitable for contraception, hormone substituting therapy, antiinflammation, promoting in vitro fertilisation, dermatological therapy and/or cosmetological treatment and the compositions may be used for these purposes.

The hormone component and the homocysteine level reducing component may be administered separately, but it is preferred to administer the active components in the form of one composition. No such compositions are available on the market at the present.

On the basis of the above recognition we have come to the following unexpected results

- the pharmaceutical compositions containing gestogen type steroid hormones increase the homocysteine concentration of the plasma, meaning the increase of the risk of thromboembolic diseases
- the increased plasma homocysteine level due to a medicine containing gestogen type hormone can especially efficiently be reduced by folic acid and vitamin B_6. We note that on the basis of data having been available for us before our investigations, one could not come to the conclusion that vitamins B would be efficient against hyperhomocysteinaemia induced by medicines comprising gestogen type hormones, as folic acid and vitamin B_6 are not efficient in all types of hyperhomocysteinaemia. *(Hong SY, Yang DH, Chang SK: Plasma homocysteine, vitamin B_6, vitamin B_{12} and folic acid in end-stage renal disease during low-dose supplementation with folic acid. Am J Nephrol 1998, 18:367-372.)*.
- In hyperhomocysteinaemia induced by medicines comprising gestogen type hormones the folic acid and vitamin B_6 therapy results in a much more intensive plasma homocysteine level reduction than it could have been expected on the basis of the prior art. According to the prior art in case of folic acid therapy against folic acid deficiency, the plasma homocysteine concentration is diminished on an average by 45 to 50% and in case of hyperhomocysteinaemia of genetic origin on an average by 20 to 25 %. *(Guttormsen AB, Schneede J, Ueland PM, Refsum H. Kinetics of total plasma homocysteine in subject with hyperhomocysteinemia due to folate or cobalamin deficiency. Am J Clin Nutr 1996, 63:194-202.)*.

The advantage of the pharmaceutical composition(s) according to the invention and of the use thereof against compositions containing only hormone is the smaller risk of thromboembolic side effects. The use of gestogen type hormones becomes safer by the pharmaceutical composition(s) according to the invention and one can expect that for patient groups (smokers, patients above the age of 35, patients

suffering from overweight, in case of anamnestic data etc.), who were excluded from the use of compositions containing solely hormone, said pharmaceutical composition(s) can be prescribed. A further advantage is that both the hormone(s) and the compounds reducing the plasma homocysteinaemia concentration will be finished in one dosage unit (tablets, capsules, ampoules, powder, solution, granules, syrup etc.) ensuring thereby the simultaneous application of the hormone active ingredient and the „antidote" acting against the most important side effect of the hormone, i.e. the plasma homocysteine reducing agent. The hormone component(s) and the plasma homocysteine level reducing compound(s) may be applied in separate dosage units as well, as according to our test results both in case of simultaneous and separate administration, hyperhomocysteinaemia induced by gestogen hormones may be reduced or prevented.

The invention accordingly further provides a method for treating patients, taking medicines containing gestogen type hormone(s), by the administration of a pharmaceutical composition according to the invention at an effective dosage or by the administration of plasma homocysteine content reducing agents, selected from folic acid, vitamin B_6, vitamin B_{12}, betaine, choline, acetyl cysteine and metabolic precursors, analogues and/or derivatives thereof in addition to the gestogen containing pharmaceutical composition.

The effective dosage is generally in the range of from 100 microgram to 9 gram per day of plasma homocysteine content reducing agents (for example it ranges from 0.5 mg to 5 mg per day of folic acid, from 10 mg to 300 mg of vitamin B_6, from 300 microgram per day to 5 mg per day of vitamin B_{12}, from 0.5 g to 9 g per day of betaine and from 100 mg to 1 g per day of acetyl cysteine).

The effective dosage of gestogen components is generally in the range of 0.05-5 mg per day.

We illustrate our invention by the following non-limiting examples:

Example a)

47 healthy women of middle age were involved in the test, who were divided in two groups on the basis of taking or not taking contraceptives, and then their fasting plasma homocysteine concentration was measured by HPLC method. The average homocysteine content of the women obtaining entirely or partially gestogen containing contraceptive therapy (daily 1) 0.15 mg of levonorgestrelum and 0.03 mg of aethinyloestradiolum, or 2) 0.25 mg of levonorgestrelum and 0.05 mg of aethinyloestradiolum, or 3) 0.15 mg of desogestrelum and 0.03 mg of aethinyloestradiolum, or 4) 0.075 mg of gestodenum and 0.03 mg of aethinyloestradiolum, or 5) 0.25 mg of norgestinatum and 0.035 mg of aethinyloestradiolum, or 6) 0.5 mg of aethynodiolum diaceticum) was significantly higher than that of the control group.

Example b)

32 healthy women of middle age were involved in the test, who were taking oral contraceptive of gestagen content (daily 1) 0.15 mg of levonorgestrelum and 0.03 mg of aethinyloestradiolum, or 2) 0.25 mg of levonorgestrelum and 0.05 mg of aethinyloestradiolum, or 3) 0.15 mg of desogestrelum and 0.03 mg of aethinyloestradiolum, or 4) 0.075 mg of gestodenum and 0.03 mg of aethinyloestradiolum, or 5) 0.25 mg of norgestinatum and 0.035 mg of aethinyloestradiolum, or 6) 0.5 mg of aethynodiolum diaceticum). The fasting plasma homocysteine content was measured by HPLC method. We have found that the extent of increase of the plasma homocysteine content was in correlation with the daily dosage of gestogen, or we also noticed an increase of the plasma homocysteine content, when exclusively gestogen containing composition was administered to the patients. It is apparent that gestogens are responsible for the increase of the homocysteine concentration.

Example c)

We have examined 31 healthy women of middle age who obtained next to a gestogen containing contraceptive (daily 1) 0.15 mg of levonorgestrelum and 0.03 mg of aethinyloestradiolum, or 2) 0.25 mg of levonorgestrelum and 0.05 mg of aethinyloestradiolum, or 3) 0.15 mg of desogestrelum and 0.03 mg of aethinyloestradiolum, or 4) 0.075 mg of gestodenum and 0.03 mg of aethinyloestradiolum, or 5) 0.25 mg of norgestinatum and 0.035 mg of aethinyloestradiolum, or 6) 0.5 mg of aethynodiolum diaceticum) 1 or 3 mg/die of folic acid or 20 mg/die of vitamin B_6 and when the fasting plasma homocysteine concentration was measured by HPLC method, a significant ($p<0.05$) reduction (on an average by 69%) was observed. Some participants (n=14) obtained separately vitamin tablets next to the contraceptive tablets, and in other cases (n=17) the contraceptive and the folic acid or vitamin B_6 were ground to a powder, admixed and filled to cachet or capsule and the mixture thus obtained was administered. As to the plasma homocysteine concentration no difference could be shown between the two methods of administration (in separate tablets or one single formulation). During the observation period no undesired pregnancy or thromboembolic complication occurred.

Example d)

In case of 6 women during a gestogen hormone therapy, which was used in the in vitro fertilisation program (the dosage of 600 mg/die progesterone was gradually reduced during 12 weeks), the change of fasting plasma homocysteine concentration was measured by HPLC method. The result was that the plasma homocysteine concentration changed proportionately with the dosage of gestogen.

Example e)

During taking gestogen containing hormone (600 mg/die of progesterone) the fasting plasma homocysteine concentration was

measured, and the therapy was then supplemented with 1 mg/die and 3 mg/die of folic acid or 20 mg/die of vitamin B_6 by placing the hormone in the form of micronised progesterone and the vitamin B in the form of folic acid or vitamin B_6 into a capsule or cachet, which was administered. The plasma homocysteine concentration was reduced on an average by 65%.

The pharmaceutical compositions according to the invention may be prepared by methods known per se. Depending on the route of administration one can prepare tablets, vaginal tablets, capsules, granules, cachets, syrup, solution, dragées, suppositories, ampoules etc.

We can accordingly add the conventionally used solid or liquid carriers to the active ingredients. As solid carrier one may use aroma substances, lubricating agents, solubilisers, suspending agents, gliding agents, disintegrating agents, tabletting or capsulating agents, such as magnesium stearate, talc, methyl cellulose, gelatine, sodium carboxymethyl cellulose, polyvinyl pyrrolidone, lactose etc.

As liquid carriers one may use e.g. buffers, preservatives, agents controlling viscosity or osmotic pressure, emulsifiers, solubilisers, sweetening agents, such as water, cellulose derivatives, alcohols, oils or oil esters etc.

Hereinbelow we give the short description of the preparation of compositions containing the hormone and the compound reducing the plasma homocysteine concentration:

Example A: Tablets containing 1) 0.15 mg of levonorgestrelum and 0.03 mg of aethinyloestradiolum, or 2) 0.25 mg of levonorgestrelum and 0.05 mg of aethinyloestradiolum, or 3) 0.15 mg of desogestrelum and 0.03 mg of aethinyloestradiolum, or 4) 0.075 mg of gestodenum and 0.03 mg of aethinyloestradiolum, or 5) 0.25 mg of norgestinatum and 0.035 mg of aethinyloestradiolum, or 6) 0.5 mg of aethynodiolum

diaceticum were ground to powder, whereafter tablets containing 1 mg or 3 mg folic acid or 20 mg of vitamin B_6 were added in the form of powder. The mixture was filled into cachets or hard gelatine capsules.

Example B: Soft gelatine capsules containing 500 mg of micronised progesterone were opened, and tablets containing 3 mg of folic acid or 20 mg of vitamin B_6 were ground to powder. The oil content of the progesterone tablets was absorbed by the powder of the vitamin tablets and this was filled into hard gelatine capsules, sealed or packed into cachets.

Claims:

1. Pharmaceutical composition based on gestogen type hormone, comprising next to the hormone component component(s) reducing the plasma homocysteine content increased upon taking hormone.
2. Pharmaceutical composition as claimed in claim 1, comprising an efficient amount of plasma homocysteine content reducing agent selected from folic acid, vitamin B_6, vitamin B_{12}, betaine, choline, acetyl cysteine and metabolic precursors, analogues and/or derivatives thereof.
3. Pharmaceutical composition as claimed in claim 1, comprising as plasma homocysteine content reducing agent an efficient amount of folic acid.
4. Pharmaceutical composition as claimed in claim 1, comprising as plasma homocysteine content reducing agent an efficient amount of vitamin B_6.
5. Pharmaceutical composition as claimed in claim 1, comprising an efficient amount of hormone selected from progesterone type hormone(s), metabolic precursor(s), analogue(s) and/or derivative(s) thereof.
6. Use of plasma homocysteine content reducing agents selected from folic acid, vitamin B_6, vitamin B_{12}, betaine, choline, acetyl cysteine and metabolic precursors, analogues and/or derivatives thereof for the preparation of pharmaceutical composition containing gestogen type hormone(s) reducing the plasma homocysteine level.
7. Use of folic acid for the preparation of pharmaceutical composition containing gestogen type hormone(s) reducing the plasma homocysteine level.
8. Use of vitamin B_6 for the preparation of pharmaceutical composition containing gestogen type hormone(s) reducing the plasma homocysteine level.

9. Process for reducing the plasma homocysteine level, which comprises administering a pharmaceutical composition containing gestogen type hormone simultaneously or previosuly or subsequently with an effiecient amount of plasma homocysteine content reducing agent, selected from folic acid, vitamin B_6, vitamin B_{12}, betaine, choline, acetyl cysteine and metabolic precursors, analogues and/or derivatives thereof.

10. Process for reducing the plasma homocysteine level, which comprises administering a pharmaceutical composition containing gestogen type hormone simultaneously or previosuly or subsequently with an effiecient amount of folic acid.

11. Process for reducing the plasma homocysteine level, which comprises administering a pharmaceutical composition containing gestogen type hormone simultaneously or previosuly or subsequently with an effiecient amount of vitamin B_6.

12. Use of plasma homocysteine content reducing agents, selected from folic acid, vitamin B_6, vitamin B_{12}, betaine, choline, acetyl cysteine and metabolic precursors, analogues and/or derivatives thereof for reducing the plasma homocysteine content.

13. Use of folic acid for reducing the plasma homocysteine content increased by gestogen hormones.

14. Use of vitamin B_6 for reducing the plasma homocysteine content increased by gestogen hormones.

15. Method of treatment of patients taking gestogen type hormone compositons, which comprises administration of an effective dosage of a composition as claimed in claim 1.

16. Method of treatment of patients taking gestogen type hormone compositons, which comprises administration of an effective amount of plasma homocysteine content reducing agents, selected from folic acid, vitamin B_6, vitamin B_{12}, betaine, choline, acetyl cysteine and metabolic precursors, analogues and/or derivatives thereof.

INTERNATIONAL SEARCH REPORT

Inte :onal Application No
PCT/HU 00/00009

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/505 A61K31/57

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BARNABEI V.M. ET AL: "Plasma homocysteine in women taking hormone replacement therapy: The postmenopausal Estrogen/Progestin Interventions (PEPI) trial." JOURNAL OF WOMEN'S HEALTH AND GENDER-BASED MEDICINE, (1999) 8/9 (1167-1172). , XP000913564 abstract; table 3 ---	1-16
Y	GB 2 131 292 A (MORTIMER DR CHRISTOPHER H) 20 June 1984 (1984-06-20) abstract ---	1-16
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 June 2000	19/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gonzalez Ramon, N

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INTERNATIONAL SEARCH REPORT

Inte. onal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	RHODE ET AL: "Effect of Orange Juice, Folic acid, and Oral Contraceptives on Serum Folate in Women taking a Folate-Restricted Diet" JOURNAL OF THE AMERICAN COLLEGE OF NUTRITION,US,AMERICAN COLLEGE OF NUTRION, WILMINGTON, NC, vol. 2, no. 3, 1983, pages 221-230-230, XP002114784 ISSN: 0731-5724 abstract	1-16
X	BUTTERWORTH ET AL: "Improvement in Cervical Dysplasia Associated with Folic Acid Therapy in Users of Oral Contraceptives" AMERICAN JOURNAL OF CLINICAL NUTRITION,US,BETHESDA,MD, vol. 35, no. 1, January 1982 (1982-01), pages 73-82-82, XP002114785 abstract	1-16
X	WHITEHEAD ET AL: "Megaloblastic Changes in the Cervical Epithelium. Association with Oral Contraceptive Therapy and Reversal with Folic acid" JAMA THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION,US,CHICAGO,IL, vol. 226, no. 12, 17 December 1973 (1973-12-17), pages 1421-1424-1424, XP002114786 ISSN: 0098-7484 abstract	1-16

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte .onal Application No
PCT/HU 00/00009

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2131292 A	20-06-1984	NONE	